Storming the Molecular Diagnostic IP Fortress

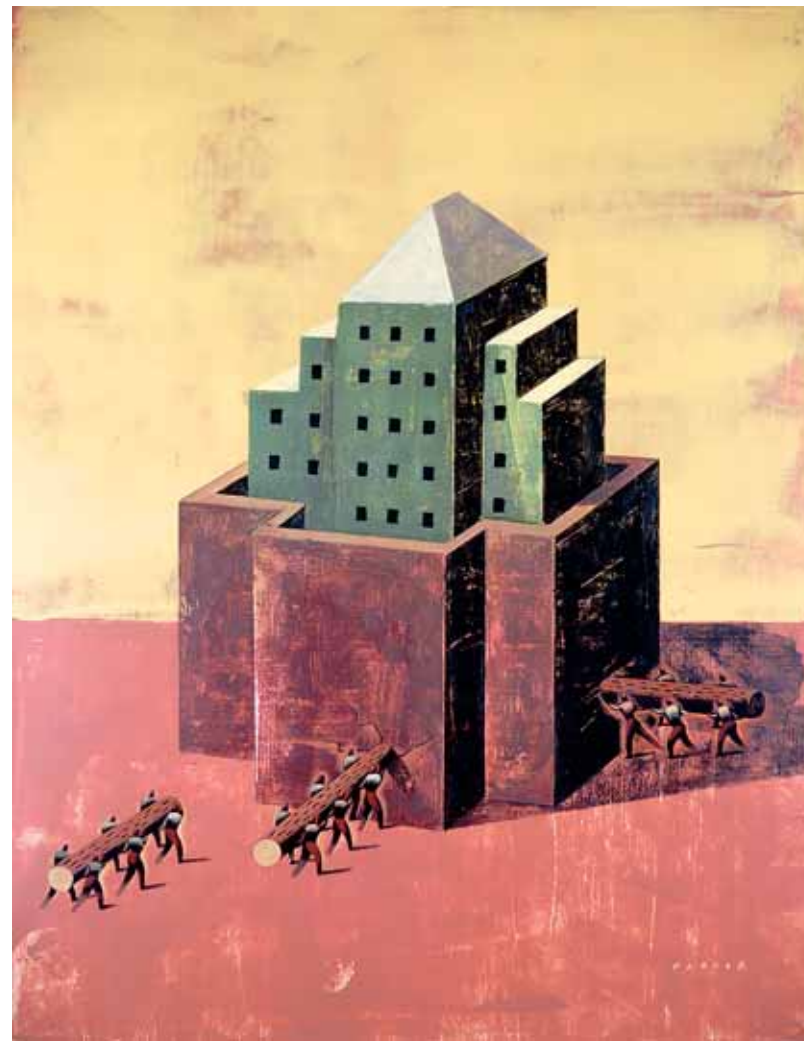
How genes are patented, and how companies control those patents through licensing, raises issues of patient access to medical tests, monopolistic business practices, ethics, lab-test quality, and the future of genetic test development. **BY MARK TERRY**

The patent can be viewed as the outer wall, or even the moat, of a fortress protecting a company's intellectual property (IP). There's no argument against the need for strong patent laws, though within biotech there is plenty of discussion about gene patents.[1] In the area of molecular diagnostics, access to IP — the drawbridges, doorways, and windows that allow users to access biotech products — causes the most difficulties, particularly in how access affects the cost of lab work and healthcare in general.

The rulers of these fortresses — those who hold the patents — have choices in how they allow access: Once the drawbridge is down, they can provide open access to all, they can charge a toll and create specific entrance criteria, or they can use an approach that lies between the two approaches. In biotech, licensing the patent is typically representative of the tolls, and how molecular diagnostic companies choose to manage licensing has significant implications for healthcare costs.

THE 99 PERCENT SCENARIO

Typically, when molecular diagnostics is discussed in the context of patents, it refers to *disease-gene patents* — literally, a patent on a genetic



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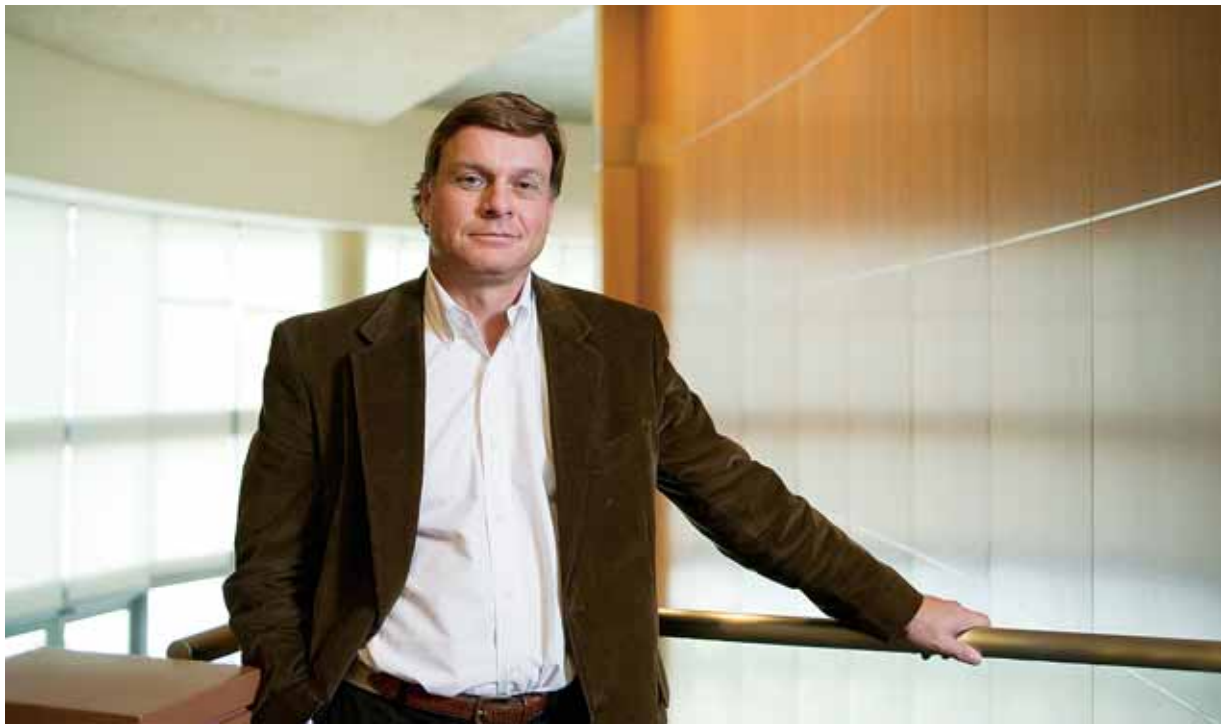
[1] Patent a *gene?* How can this be? A patent can be granted to someone who has made public something that is considered to be innovative and not obvious to specialists in a given field. It cannot be a discovery alone, thus forming the primary argument of those who oppose granting patents to scientists, universities, or others that discover genetic mutations. Gene-patient supporters counter that discoveries are more than just a basic medical discovery and are packaged with "inventive" descriptions of how the discovery can be used for diagnosis or treatment.



PHOTOGRAPH BY GARY WAGNER

"I think molecular diagnostics is going to have a huge effect on healthcare costs, which is to say I think it's going to bring them down," says Vern Norviel, partner in the Palo Alto, Calif., law firm of Wilson, Sonsini, Goodrich, & Rosati. The field of diagnostics, he says, is "the key to the next wave" in healthcare.

mutation and all associated methods of diagnosing a genetic condition. Genetic testing is one of the fastest-growing and most promising areas of molecular diagnostics. Some 90 percent of disease-gene patents are owned by the National Institutes of Health, universities, medical schools, and hospitals. Two thirds of genetic testing patents acknowledge NIH support, raising ethical questions about the lack of disclosure of research findings.

What commonly happens after discovery is a university files a patent application. Generally, the genetic discovery is far from being adaptable to a clinical test, but once the university has negotiated transfer of the patent to a company, that company's executives can approach venture capitalists to try to raise the millions of dollars needed to develop the discovery.

According to Vern Norviel, a partner in the Palo Alto, Calif., law firm of Wilson, Sonsini, Goodrich, & Rosati, and former general counsel for Affymetrix, "Getting to where something is sensitive and specific, as well as reproducible and usable, usually takes millions more dollars once they've gotten the concept to where it works. It takes a lot to get [a discovery] to where it's robust. It's an extremely difficult task."

Very often,Norviel says, diagnostic tests are started as a clinical reference laboratory product. "Either the company builds a CLIA [Clinical Laboratory Improvement Amendments] lab, or they sell components to a company like LabCorp, which will run them as a service. Hopefully, someday, they'll get it into a package that can be used by everyone, and sell it as an FDA-approved kit to clinics and physicians."

That means licensing a patent to manufacturers — the most common approach and one that typically leaves everybody reasonably happy with the outcome, from laboratory directors and hospital administrators to biotech company CEOs and venture capitalists. "There's usually very little hype," says Norviel, "and very little litigation. People really understand and respect patents as the heart of this industry. If a company does license its patents, the 99 percent scenario is that it's dealt with on a friendly basis, and if not friendly, on a quiet basis, by way of negotiation — and

it's resolved. That's how the industry really works on a day-to-day basis."

"ONE BIG GORILLA"

Allen Baum, a patent attorney and a partner with Hutchison and Mason, in Raleigh, N.C., says that there are two schools of thought in terms of how to license a test. "One is that you want to license these diagnostic tools widely and get them into as many hands as possible because you'll get more extensive use of that particular assay. The other is that you select a single vendor, through which you may get more money initially because you've got an exclusive relationship.

"The question is," he continues, "What model works best for the kind of test you're dealing with? If it's a test with broad applicability, like diagnosing elevated lipid levels, then you probably want to get it into as many hands as possible. If, on the other hand, it's a technique that's specific for a less common disease state, perhaps it's better off in the hands of one company that's very specialized in how it markets its test kits."

Some companies choose the second route, tightly controlling access to their intellectual property. Myriad Genetics, based in Salt Lake City, is often cited as the poster child for this approach because of how it has handled its patents and licensing for the BRCA-1 and BRCA-2 gene tests for susceptibility to breast and ovarian cancer. In the United States, where it holds nine patents on the BRCA-1 and BRCA-2 genes, Myriad performs the tests itself.

"Myriad has chosen to exercise its property rights by preventing anyone from performing the clinical diagnostic test," says David Korn, MD, senior vice president for research at the Association of American Medical Colleges, in Washington. "This has raised a lot of concerns in Europe and Canada, for example, where arguments of public health and equitable access at reasonable costs have been actively under debate for many, many years now." In recent years, the European Patent Office has rolled back two of Myriad's patents there on technical grounds.

Molecular diagnostics companies exercise their IP rights in various ways, some of which effectively create monopolies that prevent price competition.

The tests themselves are not difficult procedures; any laboratory set up for DNA diagnostic testing would be competent to perform them. In the case of BRCA-1 and BRCA-2, though, one might say that access to the fortress is by armed escort only. "Nothing is on the market except 'Pay us to do the test,'" says Korn. "There is no specific equipment or instrument or special reagent kit or anything of that sort. There is no product for sale. The 'product,' really, is performing the test."

Myriad is not alone in taking this approach. "Some biotech and academic institutions have licensed to only one laboratory — the only lab that does the assay — and basically, everybody has to trust it," says Jorge Leon, PhD, a former Quest Diagnostics vice president and now president of Emerson, N.J.-based Leomic Associates, where he develops commercialization strategies for new diagnostic technologies.

"The tendency right now for big biotech diagnostics companies is to not give exclusive license, or to obligate the licensees to sublicense. I would say that 75 percent of the licenses that are being given today have that caveat, that the licensee has to sublicense. The rationale is that academic centers don't want to enable one big gorilla."

The concept of exclusivity has generated a number of ethical arguments, but a practical observation is that the resulting monopoly allows a patent holder to price as it pleases, with no competition to drive costs down. Of the BRCA-1 and -2 tests, Korn says, "The experts who do similar tests think that the price of these tests — somewhere around $3,000 now — is considerably higher than it would be if someone else were allowed to offer the test."[2]

Of course, it's fair to acknowledge that those who work hard should be rewarded for their investment of time and money. "On behalf of Myriad, one has to be sympathetic to the fact that it has invested tens and tens of millions of

[2] In 2001, Myriad informed the government of British Columbia that it would enforce its BRCA-1 and BRCA-2 patents. Until then, the genetic tests had been available privately and were funded by the provincial government; enforcement meant all testing would be done by Myriad's Canadian partner, MDS Laboratories — increasing the cost from C$800 to about C$3,800 at the time. The provincial ministry of health ceased funding the test, relegating it an out-of-pocket option for women who wanted it.

dollars or more to build up enormous capability to do these tests rapidly in very large volumes," Korn says. "It has state-of-the-art labs, robotics, everything you can imagine. It made a very, very large investment to set itself up as the provider of this test for what it hoped would be the whole world. They have reason to want to recover their investment, and there's nothing wrong with that."

Korn adds that Myriad has been quite cooperative in allowing researchers to access its databases, offering testing at reduced charge for research, and permitting researchers to perform BRCA testing if they are doing so under research protocols and without charge to the patients participating in the research.

In the United States, where the fortress is much more difficult to penetrate than it is proving to be in Europe, access to it may change even without regulatory or legal persuasion. The market has a tendency to adjust itself, Leon says, "Look at BRCA-1. It's not growing as much as they need it to grow. Only 10 percent of the patients who should be tested for BRCA-1 are being tested," he points out, citing restrictive access to the test as the reason.

FOUR FLAVORS

Debra G. B. Leonard, MD, PhD, director of clinical laboratories in the department of pathology and laboratory medicine at the Weill Cornell Medical College and New York Presbyterian Hospital,[3] provides several examples of how molecular diagnostic companies have exercised their IP licensing prerogatives and some of the repercussions thereof. In several of the examples, these companies exercised their rights with cease-and-desist letters and threats of litigation.

Example #1: Sole ownership

In 1997, University of Pennsylvania Laboratories received a letter from Worcester, Mass.-based Athena Diagnostics demanding that Penn stop offering the ApoE4 molecular diagnostic test for late-onset Alzheimer's disease. At that time, Athena had an exclusive license from Duke University — which held the original patent — and controlled all access to the test, requiring that it be performed only through Athena's facilities. For this service, Athena charged $195 per specimen. Penn had been offering the test for $100.50.

Example #2: IP rights fee plus royalty

The following year, SmithKline Beecham Clinical Laboratories sent Penn a cease-and-desist letter, demanding that it stop offering a test for hereditary hemochromatosis. Progenitor, of Hackensack, N.J., owned the patent and had licensed it exclusively to SmithKline Beecham. Penn was told it could continue to offer the test if it paid an up-front fee of $25,000 for IP rights, plus an additional fee for each test performed.

Example #3: Royalty stacking

In 1999, Penn received a letter from Miami Children's Hospital, requiring it to apply for a license to perform tests for Canavan disease — a screening for which Miami Children's Research Institute held the patent. The institute charged $12.50 per test. The problem here, says Leonard, was that the test for Canavan disease is typically part of a suite of tests for people of Jewish ancestry — called the Jewish Panel — which also included tests for cystic fibrosis and Gaucher disease. Although the charge for the CF test was only $2 and that for Gaucher disease was $5, having exclusive control of one part of the Jewish Panel effectively shifted the business for the entire panel to Miami. Just to make sure it was a deal Penn couldn't refuse, the institute added two more caveats: There was a likelihood that volume limitations would be placed on the Canavan test, and Miami put a time limit on sign-up and indicated it "may be prevented by contract from licensing any latecomers."

Example #4: Nonexclusive, worldwide, in-house diagnostic testing licenses

In 1999, the University of Michigan Medical School informed Penn that it owned the licenses to a test for cystic fibrosis, specifically the cystic fibrosis delta F508 deletion cDNA mutation. Michigan was offering a nonexclusive, worldwide testing license as long as Penn offered "diagnostic results to patients at cost, or [if] reagents for the tests are obtained from one of our current product licensees … no license will be necessary."

As is clear from these examples, how a diagnostics company handles its property rights not only affects whether institutions can offer a test — and, in some cases,

[3] At the time of examples 1,2, and 3, Leonard was director of molecular pathology at the University of Pennsylvania.

whether patients will have access to a test — but also dramatically affects the cost of the tests.

GANSKE-FRIST AMENDMENT

In 1996, Congress passed an amendment to U. S. patent law, known as the Ganske-Frist Amendment. The amendment was in response to an unsuccessful lawsuit brought by an ophthalmologist who had developed an eye-surgery technique using a particular V-shaped incision. The ophthalmologist claimed that another physician who had used this type of incision had infringed on his patent.

The amendment, says Korn, "stated that physicians who practiced the procedure could not be sued for patent infringement. You have the patent, but you can't enforce it."

It essentially exempts a physician and his or her institution — clinic, hospital, HMO, or other "related health care entity" — from liability for damages or an injunction for infringing a patent while performing a "medical activity." The amendment defines medical activity as "the performance of a medical or surgical procedure on a body," but it excludes medical testing from the definition with the following clause: "The use of a patented machine, manufacture, or composition of matter in violation of such patent, the practice of a patented use of a composition of matter in violation of such patent, or the practice of a process in violation of a biotechnology patent." The amendment does not define a biotechnology patent.

Mark Sobel, MD, PhD, executive officer for the American Society for Investigative Pathology and the Association for Molecular Pathology, based in Bethesda, Md., says, "They made an exception, but then they made an exception to the exception. They said, 'For medical practice we'll make an exception, but if it's diagnostic testing we won't give you the exception.' Why is that? In my opinion, there was a big lobbying effort by various forces to deny the exception to the diagnostic testing field."

> **"One can imagine that if many others decided to patent their mutation and monopolize the testing practice, all kinds of problems would arise."**
>
> *— David Korn, MD*

Litigation is continuing in many areas of molecular diagnostics and will continue to shape how licensing is applied.

A LONG ROAD

At the moment, how genes are patented and how companies exercise those patents by licensing has an important and striking effect on patients' access to medical testing, ethical issues, anticompetitive and monopolistic business practices, laboratory testing quality control, and the future of medical test development. A few laboratories have been driven out of some test markets and laboratory testing prices have been pushed upward.

Says Korn, "Nothing would prevent a company from attempting to do the same thing — restricting their licenses — with any gene of interest. As we learn more and more about the relationship of specific genes and specific variations, mutations, and the like, there are going to be many, many tests for all kinds of things. They are going to be disease-predictive, they are going to predict one's toxic response to a drug, and so on. We are at the dawn of genetic testing, not the zenith or the nadir — this is just the beginning. And one can imagine that if many others decided to patent their mutations and then monopolize the practice of those tests, it would be very, very difficult — all kinds of problems would come up."

Many of these tests will be valuable clinically to people and populations. Some will predict disease, allowing patients to be treated earlier and with less suffering and expense. Pharmacogenetics is in its infancy, but already labs are offering tests to determine whether a drug will be effective for a certain condition — thus averting trial-and-error treatment regimens and the cost of negative side effects. How payers ultimately view the value of these tests may depend on how access to them influences their cost.

Norviel is optimistic. "Molecular diagnostics is going to have a huge effect on healthcare costs, which is to say I think it's going to bring them down — with the reason being that the field of diagnostics is the key to the next wave." BH

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